UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

May 29, 2002

MEMORANDUM

FROM: Kathryn Boyle, CoChair IIFG

and

Kerry Leifer, CoChair IIFG

TO: Robert Forrest, Chief
Minor Use, Inerts, and Emergency Response Branch

SUBJECT: IIFG Decision Memo

Please find attached the Inert Ingredient Focus Group recommendations for the inert ingredients associated with cellulose and paper.

INERT INGREDIENT FOCUS GROUP

DECISION DOCUMENT for

Cellulose and Paper

Petition No.: no

Tolerance Reassessments?: yes

Chemical Substance	**CAS Reg. No.**	**40 CFR 180.1001 citation**
alpha - cellulose		(c)(e)
croscarmellose sodium (a cross-linked form of sodium carboxymethyl cellulose)	74811-65-7	(c)
sodium carboxymethyl cellulose	9004-32-4	(c)
Paper fiber, deinked or recycled, conforming to 21 CFR 109.30(a)(9) and 21 CFR 176.260		(d)
Paper fiber, produced by the kraft (sulfate) or sulfite pulping processes.		(d)

Other chemicals considered in this assessment are: methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and cellulose acetate. The tolerance exemptions for these chemicals have been previously reassessed and are included in this assessment only for their structural similarities to cellulose and to consider for List 4A classification.

HPV Chemical? No

Use Pattern (pesticidal): Cellulose can be used as a solid diluent, carrier, and suspending agent. Cellulose derivatives are used as suspending agents, surfactants, thickeners, and dispersing agents in food and cosmetics. Cellulose acetate is used as a pesticide rate release regulating agent. Paper is used as a carrier.

Use Pattern (non-pesticidal): Cellulose and cellulose derivatives are used as a both direct and indirect food additives. As direct food additives they are used in baked goods and baking mixes, fats and oils, cheese, meat and poultry products, sweet sauces, toppings, syrups, gelatins, puddings and fillings, gravies, dairy product analogs, candy and chewing gum. As indirect food additives they are used as substances migrating to food from food packaging. The cellulose derivatives are used in cosmetics such as hair products, eye and facial makeup and skin care preparations. They can also be used in surface coatings, as polymerization additives, in adhesives, and in detergents and cleaners. Croscarmellose sodium is used as a disintegrating agent in pharmaceuticals (tablets). Cellulose fibers are used as a component of insulation.

1. Introduction:

Cellulose, or alpha-cellulose, is a naturally-occurring polymeric material. It can also be referred to as a macromolecule or polysaccharide. Chemically, cellulose is a long chain of glucose molecules that are linked with beta (1- 4) glycosidic bonds. The molecular weight of isolated cellulose as reported by FDA is approximately 50,000 daltons. Cellulose is part of the plant cell wall of wood, cotton, and various plant crops consumed for nutrition. It is the most abundant carbohydrate in nature. Dietary cellulose (i.e., fiber) from edible plants is consumed by humans on a daily basis. Humans do not possess the enzyme necessary to break the beta (1- 4) glycosidic bond; thus, cellulose passes unchanged through the intestinal tract. The Dietary Guidelines for Americans published by the USDA (United States Department of Agriculture) recommend eating foods with adequate fiber. The National Cancer Institute recommends that an individual consume 20 to 30 grams of fiber each day with an upper limit of 35 grams per day.

The derivatives are not naturally occurring materials, but are manufactured from cellulose. These are polymeric substances with high molecular weights: the information available indicates ranges of 40,000 to 480,000 daltons depending on the degree of polymerization

Paper is manufactured by applying a watery suspension of cellulose fibers, known as pulp, to a screen thus allowing the water to drain and leaving the fibrous particles behind in a sheet. Pulp is produced by digesting a cellulose containing material into its fibrous constituents via chemical and/or mechanical means. In the case of wood, the most common pulping material, chemical pulping actions release cellulose fibers by selectively destroying the chemical bonds in the glue-like substance (lignin) that binds the fibers together. The two major chemical pulping processes used in the US are kraft/soda pulping and sulfite pulping. Kraft pulping produced 80 percent of all US pulp tonnage during 1993. After the pulping process, dependent on the type of paper desired, paper manufacturing includes various processes to separate and remove impurities, bleaching and coloring processes to achieve the desired color, adding various resins or texture materials depending on the desired end-result, and drying by pressing and heating to bond the fibers.

The following information was used in performing this assessment: The available information consisted of information retrieved from various websites, such as,

- EPA (www.epa.gov)
- TOXNET (www.toxnet.nlm.nih.gov.)
- World Health Organization (WHO) (jecfa.ilsi.org/section1.htm) and (www.inchem.org/document/jecfa/jecmono/v26je08.htm)

and those websites containing descriptions of cellulose and paper.

Additionally, the following documents were used:

- GRAS (Generally Recognized as Safe) Food Ingredients - Cellulose and Derivatives were evaluated in a 1972 assessment by FDA.
- Certain Cellulose Derivatives as Food Ingredients were evaluated by the Food and Drug Administration (FDA) in a 1974 assessment.
- Final Report on the Safety Assessment of Hydroxypropylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropylmethylcellulose, and Cellulose Gum: Cosmetic Ingredient Review Journal of the American College of Toxicology Vol. 5 No. 3 (1986)

2. Chemical Specific Uses of Cellulose and Cellulose Derivatives:

Microcrystalline cellulose is obtained by treating alpha cellulose with mineral acids. It is used to convert liquid foods to granular forms or smooth-spreading gels, and as an anticaking or binding agent.

Methyl cellulose is used as a thickener, stabilizer, emulsifier, bodying or bulking agent, and binder in foods. It was first used in foods in the US in 1960.

Carboxymethyl cellulose and it sodium salt (sodium carboxymethyl cellulose or cellulose, carboxymethyl ether, sodium salt are used as thickening agents and stabilizers in foods. Little distinction is made between the two chemicals. Both were first used in foods in the US in 1945.

Hydroxypropylmethyl cellulose is used as a thickening agent, stabilizer, and emulsifier.

Ethyl cellulose is used as a coating for vitamin preparations, as a binder and filler, and as a component of paper and paperboard food packaging materials. It is in hard candy and chewing gum.

3. FDA's Conclusions

There is a large toxicity database for cellulose and its derivatives. It includes acute, subchronic, chronic/carcinogenic, and reproductive studies. The metabolism and absorption has been well-documented.

FDA's overall conclusion is as follows:

"Cellulose is a major constituent of many foods of plant origin. As such it is a significant portion of the diet, but is neither degraded nor absorbed. Cellulose derivatives considered in this report are virtually unabsorbed and little or no degradation of absorbable products occurs in the human digestive tract. In man, consumption of large amounts appears to have no effect other than providing dietary bulk, reducing the nutritive value of such foodstuffs and possibly exerting a laxative effect."

FDA's chemical-specific hazard conclusions are as follows:

Cellulose and Microcrystalline Cellulose

"There is no evidence in the available information on pure and regenerated cellulose, including microcrystalline cellulose, that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current, or that might reasonably be expected in future."

Methyl Cellulose

"In humans, virtually 100 percent of orally ingested methyl cellulose can be recovered in the feces within four days, indicating that absorption does not occur. However, in pregnant mice, very high doses of methyl cellulose, while not teratogenic, cause a significant increase in maternal mortality and retardation of fetal maturation."

According to the summary of the study in the FDA Assessment pregnant rats, hamsters, and mice were administered doses of methyl cellulose in corn oil. In rats at doses up to 1320 mg/kg/day for 10 consecutive days, there was no clearly discernible effect on nidation or on maternal or fetal survival. In hamsters, doses of up to 1000 mg/kg/day for five days (gestation days 6 to 10) did not produce significant effects on nidation (fertilization) or on maternal or fetal survival.

Daily doses of up to 345 mg/kg/day from day 6 through day 15 of gestation in mice had no clearly discernible effect on nidation or on maternal or fetal survival. However, doses of 1600 mg/kg/day caused a significant increase in mortality in treated dams and a decrease in the pregnancy rate of survivors. There was a marked increase in the number of resorption sites. The live fetuses were smaller and exhibited significant retardation in maturation. The findings resembled those produced by high molecular-weight polysaccharides such as the vegetable gums. The dose of 1600 mg/kg/day is higher than that tested in either the rat or hamster. It is possible that the effects could be due to nutritional deficiencies due to deliberately high doses of indigestible material.

Information in the FDA assessment indicated that the average daily intake for cellulose deliberately added to foods ranged from 48 to 360 mg/kg/day (1970s). Cellulose derivatives were at significantly lower levels and ranged from less than 1 to 36 mg/kg/day. It is unlikely that levels

of human consumption of methyl cellulose would reach levels comparable to those at which effects were seen.

Carboxymethyl Cellulose and Sodium Carboxymethyl Cellulose

"Because carboxymethyl cellulose becomes the sodium salt in the presence of sodium ion, no distinction between the two substances as used in food need be made." There is no evidence to suggest that either chemical substance would be a hazard to the public when used at levels that are now current or that might reasonably be expected in the future."

Hydroxypropylmethyl Cellulose

"There is no evidence in the available information on hydroxypropylmethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced" (thickening agent, stabilizer and emulsifier). Given the nature of the chemical substance, the use pattern specified above as a food additive is very likely to also be the use pattern for pesticide products."

Hydroxyethyl Cellulose

In the FDA assessment, there is less toxicity information available for hydroxyethyl cellulose than for other cellulose derivatives. However, given the chemical similarities of the derivatives, there is no reason to believe that this cellulose derivative should interact with the human body with any significant difference. All cellulose derivatives examined are of low toxicity; therefore, hydroxyethyl cellulose should also be of low toxicity.

Cellulose Acetate

In the FDA Assessment, cellulose acetate was only examined for use as a food packaging material. It was concluded that: "There is no evidence in the available information ..... that demonstrates or suggests reasonable grounds to suspect, a hazard to the public when ..... used in food packaging materials as now practiced or as they might be expected to be used for such purposes in future."

TOXNET indicated that cellulose acetate is an amorphous white solid material in granular, flake, or powder form from which fibers can be formed by extrusion. It is a thermoplastic material and can be heat-set or extruded. The OSHA (Occupational Safety and Health Administration) Chemical Sampling Information Form contains no exposure limits or health factor concerns.

The establishment of the tolerance exemption for cellulose acetate in 1995 was based on its conformance with the polymer exemption guidance criteria.

4. World Health Organization (WHO)

Cellulose derivatives have been examined at eight meetings of the FAO/WHO Joint Expert Committee on Food Additives (JECFA). Various toxicological studies (acute, chronic/carcinogenic, reproduction, mutagenicity, metabolism and absorption, and observations in man were discussed for: ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, methylethyl cellulose, and sodium carboxymethyl cellulose. The human observations concerned the laxative effects of modified celluloses.

The conclusion was reached that cellulose derivatives have "a low toxicity." The estimate of acceptable daily intake is "not specified", which is defined as:

> A term applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of JECFA, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance

The only concern specified was that the ability to produce laxation should be taken into account when using these substances as food additives.

5. SAR Assessment

Several of the cellulose derivatives were evaluated by the SAR (structure activity relationship) process. Both sodium carboxymethyl cellulose and ethyl hydroxyethyl cellulose were rated as low concern for both human health and ecotoxicity concerns. Hydroxypropylmethyl cellulose and methyl cellulose were only rated for human health, for which they were rated as low concern.

6. Paper Assessment

The tolerance exemption for paper was established on April 14, 1988 (53 FR 12418) (FRL-3365-8). The rationale for establishing the tolerance exemption included its similarities to other cellulosic materials already cleared under 40 CFR 180.1001(c), and the fact that pulp is cleared under 21 CFR 186.1673 as an indirect food substance affirmed as generally recognized as safe (GRAS).

The Agency no longer uses comparisons to similar materials as the basis for action unless the materials have already undergone the tolerance reassessment process and have been determined to be reassessed. In this case, the similar materials alpha-cellulose, oat hulls, shells (almond, cocoa, coconut, and walnut), and wood flour have already been reassessed, or in the case of alpha-cellulose is being reassessed in this document. As explained previously paper is mostly cellulose fibers. Paper is derived from pulp. Pulp is derived mostly from wood.

The tolerance exemption for de-inked and/or recycled paper was established on August 1, 1989 (54 FR 31674) (FRL-3623-5). Paper that is to be recycled must first be de-inked, that is, the ink as well as the various coatings and additives are separated from the fibers (such as cellulose) that form the structure of paper. It is the cellulose fibers that are recycled. These fibers are then combined with fibers that have not been previously made into paper.

The rationale for establishing the de-inked and/or recycled tolerance exemption included the above tolerance exemption for paper, and the fact that pulp from reclaimed paper is cleared under 21 CFR 176.260 as a component of articles used in producing, processing, preparing, treating, packaging, transporting, or holding food subject to certain provisions.

It is not expected that residues of paper when used as a carrier (the use that would be expected due to the nature of paper) would be present in raw agricultural commodities. When applied to crops, paper would not be expected to be absorbed by the plant.

7. Croscarmellose Sodium

Croscarmellose sodium is a cross-linked carboxymethylcellulose sodium that is sometimes referred to as sodium cellulose glycolate. The cross-linking reduces its water solubility and permits the material to swell and take up many times its weight in water. These properties make croscarmellose sodium similar to those of sodium starch glycolate, a cross-linked potato starch derivative. Sodium starch glycolate is produced by crossing-linking and carboxymethylation of potato starch. Both chemicals are used as disintegrants (disintegrating agents) in the pharmaceutical industry.

The only concern for either of these chemicals would be for inhalation of respirable particles (less than 10 microns). Since either of these materials can absorb many times their own weight in water and swell (in volume), inhalation of respirable particles may lead to lung effects. However, these concerns can be addressed by the acute end-product toxicity testing performed at the time of product registration.

8. Hazard Characterization:

Other than the inhalation concerns for croscarmellose sodium, there is no available information on any of the chemicals considered in this document indicative of a hazard or significant adverse effects - to the general public or any population subgroup. There have been

many reviews of these materials by organizations such as FDA and WHO. The available information indicate that these chemical substances pass through the intestinal tract unabsorbed. They are of low toxicity.

9. Type of risk assessment: qualitative

10. Sensitivity of Infants and Children:

These chemicals have low toxic potential. In addition, humans of all ages are highly exposed to them from natural and anthropogenic sources. At this time, there is no concern for potential sensitivity to infants and children. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary.

11. Fate Assessment:

Cellulose derivatives would undergo biological degradation in a matter of days to weeks, and ultimate degradation to carbon dioxide and water in a matter of weeks to months. In water, partitioning to the sediment is likely; therefore, celluloses would be expected to be found in the sorbed state in water. Transport to surface in the sorbed state would dominate the non-degradation pathways of dissipation. Groundwater contamination is not likely to be significant, given the partitioning to the sediment.

12. Ecotoxicity Assessment

Cellulose derivatives would be practically non-toxic to aquatic organisms. Terrestrial animal toxicity based on the available data would indicate cellulose derivatives are practically non-toxic on an acute basis.

13. Cumulative Exposure:

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Cellulose and its derivatives are structurally related; however, all are low toxicity chemicals. Therefore, the resultant risks separately and/or combined should also be low. EPA does not have, at this time, available data to determine whether these chemicals have a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment.

14. IIFG Recommendations:

By consensus there were no objections to the following:

The following tolerance exemptions are reassessed: In 40 CFR 180.1001 (c) alpha cellulose, croscarmellose sodium, and sodium carboxymethylcellulose. In 40 CFR 180.1001 (d) Paper fiber, deinked or recycled, conforming to 21 CFR 109.30(a)(9) and 21 CFR 176.260, and Paper fiber, produced by the kraft (sulfate) or sulfite pulping processes. In 40 CFR 180.1001 (e) alpha-cellulose.

Given the non-toxic nature of cellulose and its derivatives, the following List reclassifications are made or confirmed:

cellulose (CAS Reg. No. 9004-34-6, 65996-61-4): List 4A
cellulose acetate (CAS Reg. No. 9004-35-7: List 4A
carboxymethyl cellulose (CAS Reg. No. 9000-11-7): List 4A
hydroxypropylmethyl cellulose (CAS Reg. No. 9004-65-3): List 4A
methyl cellulose (CAS Reg. No. 9004-67-5): List 4A
sodium carboxymethyl cellulose (CAS Reg. No. 9004-32-4, 51395-75-6): List 4A

Given the derivation of paper from cellulose, the history and nature of paper, and the role that it plays in our daily lives, the List 4A reclassifications are reconfirmed for paper.

Croscarmellose sodium is classified as List 4B, due to the inhalation concerns.

Tolerance exemptions (with List 4A classification) may be established for:

ethyl cellulose (CAS Reg. No. 9004-57-3)
hydroxyethyl cellulose (CAS Reg. No. 9004-62-0)
cellulose, regenerated (CAS Reg. No. 68442-85-3)
hydroxypropyl cellulose (CAS Reg. No. 9004-64-2).
ethyl hydroxyethyl cellulose (CAS Reg. No. 9004-58-4)

Attachment:

EFED review (Abel; April 10, 2002)